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VALIDATION OF THE ALTERNATIVE INTERNATIONAL PROGNOSTIC SCORE-E (AIPS-E): ANALYSIS OF BINET STAGE A CHRONIC LYMPHOCYTIC PATIENTS ENROLLED INTO THE O-CLL1-GISL PROTOCOL

Running title: VALIDATION OF THE AIPS-E IN BINET A STAGE CLL CASES.

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0984-681329; Fortunato Morabito, MD, Biotechnology Research Unit, Aprigliano, A.O./ASP of Cosenza, 87100, Cosenza, Italy, Department of Hematology and Bone Marrow Transplant Unit, Augusta Victoria Hospital, Jerusalem, Israel. Tel n +393929785568. E-mail: f.morabito53@gmail.com

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Novelty statements

- An extraordinary heterogeneity of clinical course characterizes chronic lymphocytic leukemia.
- Recently, both AIPS-E and IPS-E scores have been proposed to help the attending physician refine individual patient's prognosis.
- Our data confirm an accurate prognostic utility of both AIPS-E and IPS-E at the individual patient level.
- These data may be useful to regulate the follow-up plans for Binet stage A CLL patients.

Abstract

Objectives

To validate the predictive value on time to first treatment (TTFT) of AIPS-E and IPS-E evaluated in an independent cohort of newly diagnosed and non-referred Binet stage A CLL patients enrolled in the O-CLL1-GISL protocol (clinicaltrial.gov identifier: NCT00917540).

Methods

A cohort of 292 newly diagnosed Binet A CLL cases has been enrolled in the study. Patients from several Italian Institutions were prospectively enrolled within 12 months of diagnosis into the O-CLL1-GISL protocol

Results

The majority of patients were male (62%); median age was 60.4 years, 102 cases (34.9%) showed unmutated *IGHV* genes, 8 cases (2.8) the presence of del(11q)/del(17p), 142 cases (48.6%) the presence of palpable lymph nodes and 146 cases (50%) and ALC >15x10^9/l. After a median follow-up of 7.2 years, 130 patients underwent treatment.

According to the AIPS-E, 96 patients were classified as low-risk, 128 as intermediate-risk, and 68 as high-risk. These groups showed significant differences in terms of TTFT. The C-statistic was 0.71 (P<0.0001) for predicting TTFT. According to IPS-E, 77 patients were classified as low-risk,

135 as intermediate-risk, and 80 as high-risk. These groups showed significant differences in terms of TTFT. The C-statistic was 0.705 (P<0.0001) for predicting TTFT.

Conclusions

Our data confirm an accurate prognostic utility of both AIPS-E and IPS-E at the individual patient level. These data may be useful for a precise stratification of early-stage patients.

Introduction

Condoluci et al. [1] recently proposed a clinical score for newly diagnosed, asymptomatic, Binet stage A chronic lymphocytic leukemia (CLL) patients based on an extensive international effort. Combining absolute lymphocyte count (ALC) >15 x 10^9/l, unmutated immunoglobulin heavy-chain variable region (*IGHV*) gene, and presence of palpable lymph nodes as risk factors, they realized the International Prognostic Score for Early CLL patients (IPS-E), which allowed of segregating early-stage patients in terms of time to first-line treatment (TTFT).

Smolej et al. [2], who have validated the predictive value of the International Prognostic Score-E (IPS-E), recently proposed by Condoluci et al. [1], on time to first treatment (TTFT) of 130 Binet stage A chronic lymphocytic leukemia (CLL) cases. They also have proposed and externally validated a modified IPS-E, called Alternative IPS-E (AIPS-E), in a cohort of 388 Binet stage cases in which the presence of palpable lymph-nodes as a predictor is substituted for by that of del(11q)/del(17p). [2] This approach may overcome the individual inter-observer variability in the evaluation of slightly enlarged external lymph nodes. Here, AIPS-E and IPS-E were evaluated in an independent cohort of newly diagnosed and non-referred Binet stage A CLL patients enrolled in the O-CLL1-GISL protocol, and the conclusion was reached that both scores are capable of an accurate prediction of the subsequent course of early stages CLL patients.

METHODS

Patients

Newly diagnosed CLL patients from several Italian Institutions were prospectively enrolled within 12 months of diagnosis into the O-CLL1-GISL protocol (clinicaltrial.gov identifier: NCT00917540). Recruitment began in January 2007, and the criteria for CLL diagnosis employed followed the 1996 NCI/WG guidelines requiring >5,000 lymphocytes/μL in the peripheral blood.[3] CLL cell phenotype, CD38, and ZAP-70 expression, and *IGHV* mutational status were performed in a central laboratory in Genova, while all FISH and genetic analyses were performed in Milan. This study was approved by the ethics committees from each participating center. All patients provided written informed consent to participate in the study.

To date, the study has enrolled 492 CLL patients. Since this observational trial started in 2007 and CLL diagnosis and staging were based on the NCI-WG 1996 guidelines,[3] a significant fraction of cases (150/492; 30.5%) included in our cohort would be reclassified as clinical monoclonal B-cell lymphocytosis (cMBL) by IWCLL 2008 guidelines.[4] Excluding these 150 cMBLs, 292 of the remaining 342 cases, having all four variables (*IGHV* mutational status, FISH, presence of palpable lymph nodes, and absolute lymphocyte count) included in the AIPS-E and IPS-E,[1,2] were included in this analysis.

Assessment of biological markers

Cytogenetic abnormalities involving deletions at chromosomes 11q23 and 17p13 were evaluated by FISH on a purified $CD19^+$ population.[5] *IGHV* mutational status was assessed using cDNA.[6] Sequences were aligned to the IMGT directory and analyzed using IMGT/VQUEST software.

Indications for therapy

All patients underwent follow-up visits every 6 months. All physicians used the NCI/WG guidelines as a reference criterion for starting therapy[1,2,] and all patients had a minimum follow-up of 6 months TTFT.

IPS-E and AIPS-E

The IPS-E model was calculated giving points to absolute lymphocyte count (ALC) (1 point for cases with ALC>15 x 10^9/l), immunoglobulin heavy-chain variable-region (*IGHV*) gene (1 point for cases with unmutated status), and palpable lymph nodes (1 point for cases with presence of palpable lymph nodes). Patients were grouped into low-risk (score 0), intermediate-risk (score 1) and high-risk (score 2-3) (Table 1).[1]

The AIPS-E model was calculated giving points to del(11q)/del(17p) [(1 point for cases with presence of del (11q)/del(17p)], immunoglobulin heavy-chain variable-region (*IGHV*) gene (1 point for cases with unmutated status), and absolute lymphocyte count (ALC) (1 point for cases with ALC>15 x 10^9/l). Patients were grouped into low-risk (score 0), intermediate-risk (score 1) and high-risk (score 2-3) (Table 1).[2]

Statistical analysis

For categorical variables, statistical comparisons were performed using two-way tables for the Fisher's exact test and multi-way tables for the Pearson's Chi-square test. TTFT was calculated from diagnosis (i.e., the index date) to the start of the first CLL treatment. Cases without an event were censored at the time of the last observation. TTFT analyses were performed using the Kaplan-Meier method. Statistical significance of associations between individual variables and TTFT was calculated using the log-rank test. Univariate and multiple Cox regression analyses identified the independent correlates of the outcome variable. A value of $P<0.05$ was considered statistically significant. Harrell C-statistics were calculated to evaluate further the discriminatory value of the progression-risk score (c=1 indicates perfect discrimination; c=0.5 indicates a complete absence of prognostic accuracy). The Harrell C-statistic was performed using STATA version 9; all the other analyses were performed using SPSS Statistics 21.

Results

A total of 292 CLL patients were included in this analysis. The majority of patients were male (62%); median age was 60.4 years (range 30-70 years), 102 cases (34.9%) showed unmutated *IGHV* genes, 8 cases (2.8) the presence of del(11q)/del(17p), 142 cases (48.6%) with the presence of palpable lymph nodes and 146 cases (50%) an absolute lymphocyte count (ALC) >15 x 10^9/l (Table 2 lists baseline patient features). After a median follow-up of 7.2 years (range, 3 months-10.9 years), 130 patients were treated.

First, we assessed the relationship between AIPS-E and TTFT (Table 3). In particular, the three factors [absolute lymphocyte count (ALC) >15 x 10^9/l, unmutated *IGHV* gene, and presence of del(11q)/del(17p)], all significantly validated by univariate analysis, were introduced into a Cox multivariate model, and their independent prognostic value was confirmed (Table 3). Second, 96 patients were classified as low risk (no risk factor present at the diagnosis), 128 as intermediate risk (with one factor), and 68 as high risk (with two to three factors) according to the AIPS-E score. These groups showed significant differences in terms of TTFT (Figure 1A). Patients with low, intermediate, and high risk had an estimated 5-year TTFT of 89.6%, 70.9%, and 35.4%. The C-statistic was 0.71 (P<0.0001) for predicting TTFT, a value that exceeds the 0.70 threshold and underscores the prognostic utility of the scoring system at the individual patient level.[3]

Thus, we assessed the relationship between IPS-E and TTFT (Table 3). In particular, the three factors [absolute lymphocyte count (ALC) >15 x 10^9/l, unmutated immunoglobulin heavy-chain variable region (*IGHV*) gene, and presence of palpable lymph nodes], all significantly validated by univariate analysis, were introduced into a Cox multivariate model, and their independent prognostic value was confirmed (Table 3). According to IPS-E, 77 patients were classified as low risk (no risk factor present at the diagnosis), 135 as intermediate risk (with one factor), and 80 as high risk (with two to three factors). These groups showed significant differences in terms of TTFT (Figure 1B). Patients with low, intermediate, and high risk had an estimated 5-year TTFT of 92.6%, 68.4%, and 47.2%. The C-statistic was 0.705 (P<0.0001) for predicting TTFT, a value that exceeds the 0.70 threshold and underscores the prognostic utility of the scoring system at the individual patient level.[3]

Discussion

Recently, Smolej et al. [2] published a study that validated the IPS-E score[1] in a cohort of unselected, non-referred, and consecutive early-stage and asymptomatic CLL patients.

Furthermore, using FISH data instead of palpable lymph nodes, they proposed an alternative scoring system (AIPS-E), showing similar results in terms of TTFT prediction to IPS-E.

Our study based on data from a multicenter cohort of newly diagnosed, asymptomatic Binet stage A CLL patients enrolled prospectively and centrally characterized for significant genetic abnormalities and cellular and molecular markers reinforces the findings of Smolej et al.[2] Our study and that of Smolej et al. [2] demonstrated the importance of FISH analysis at the diagnosis time. Although in the setting of early-stage and asymptomatic patients, we observed a low rate of cases with unfavorable FISH (del17p/del11q), the research of these cytogenetic abnormalities allows for identifying patients with more aggressive clinical courses.

Nevertheless, both scores' limitation is the availability of *IGHV* and cytogenetic data at the time of diagnosis in the clinical practice. The more recent IWCLL guidelines[7] do not recommend routine testing for IGHV and FISH at the diagnosis but only at first-line therapy. Thus, many patients could not be evaluated for these biological parameters and consequently stratified through these two scores. However, our data confirm an accurate prognostic utility of both scoring systems (AIPS-E and IPS-E) at the individual patient level.

These data may be useful for an accurate stratification of early-stage patients and for the identification of cases with an aggressive clinical course who may be candidates for novel clinical trials.

Contributions:

F.M., M.G., and M.F. designed the study; F.M., G.T., M.G., G.D.A., performed statistical analysis; F.M., M.G., G.T., M.F., E.A.M., G.F., G.C., F.R.M, A.G.R., M.C., F.F., F.D.R., A.N., R.F., F.S., S.B. analysed and interpreted data, and wrote the manuscript; all authors gave final approval for the manuscript.

Conflict-of-interest disclosure:

Nothing to disclose

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Data availability statement: The dataset generated and analysed during the current study is available from the corresponding author on reasonable request.

Figure legend

Figure 1. TTFT of the entire cohort of 292 CLL patients, according to the AIPS-E (Panel A) and according to the IPS-E (Panel B)

Table 1. IPS-E and AIPS-E

IPS-E		
	0 points	1 point
***IGHV* mutational status**	mutated	unmutated
Lymphocytes >15 x10^9/l	no	yes
Palpable lymph nodes	no	yes
Total score: 0= low-risk; score 1= intermediate-risk; score 2-3= high-risk		
AIPS-E		
	0 points	1 point
***IGHV* mutational status**	mutated	unmutated
Lymphocytes >15 x10^9/l	no	yes
del(11q)/del(17p)	no	yes
Total score: 0= low-risk; score 1= intermediate-risk; score 2-3= high-risk		

Table 2. Patient's clinical features (N=292)

Features	**No (%)**
Age, years	
<65	215 (73.6)
≥65	77 (26.4)
Sex	
Male	181 (62)
Female	111 (38)
β2-M, mg/L (N=223)	
≤3.5	217 (97.3)
>3.5	6 (2.7)
***IGHV* mutational status**	
Mutated	190 (65.1)
Unmutated	102 (34.9)
Palpable lymph nodes	
No	150 (51.4)
Yes	142 (48.6)
Lymphocytes >15x10^9/l	
No	146 (50)
Yes	146 (50)
del(17p)	
negative	290 (99.3)
positive	2 (0.7)
del(11q)	
negative	286 (97.9)
positive	6 (2.1)

Table 3. Relationship between AIPS-E, IPS-E, and TTFT: a univariate and multivariate analysis

Features	Univariate analysis		Multivariate analysis (AIPS-E code)		Multivariate analysis (IPS-E code)	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Lymphocytes >15x10^9/l	1.65 (1.1-2.21)	0.012	1.42 (1.01-2.02)	0.049	1.47 (1.04-2.09)	0.03
Unmutated IGHV	5.0 (3.98-7.16)	<0.0001	4.36 (2.98-6.36)	<0.0001	4.92 (3.43-7.05)	<0.0001
Presence of del(11q)/del(17p)	4.12 (2.61-6.51)	<0.0001	1.94 (1.2-3.13)	0.007	-	-
Palpable lymph nodes	1.49	0.042	-	-	1.48	0.049

	(1.02-2.2)				(1.01-2.18)	

Abbreviations: HR = hazards ratio; 95% CI = 95% confidence interval.

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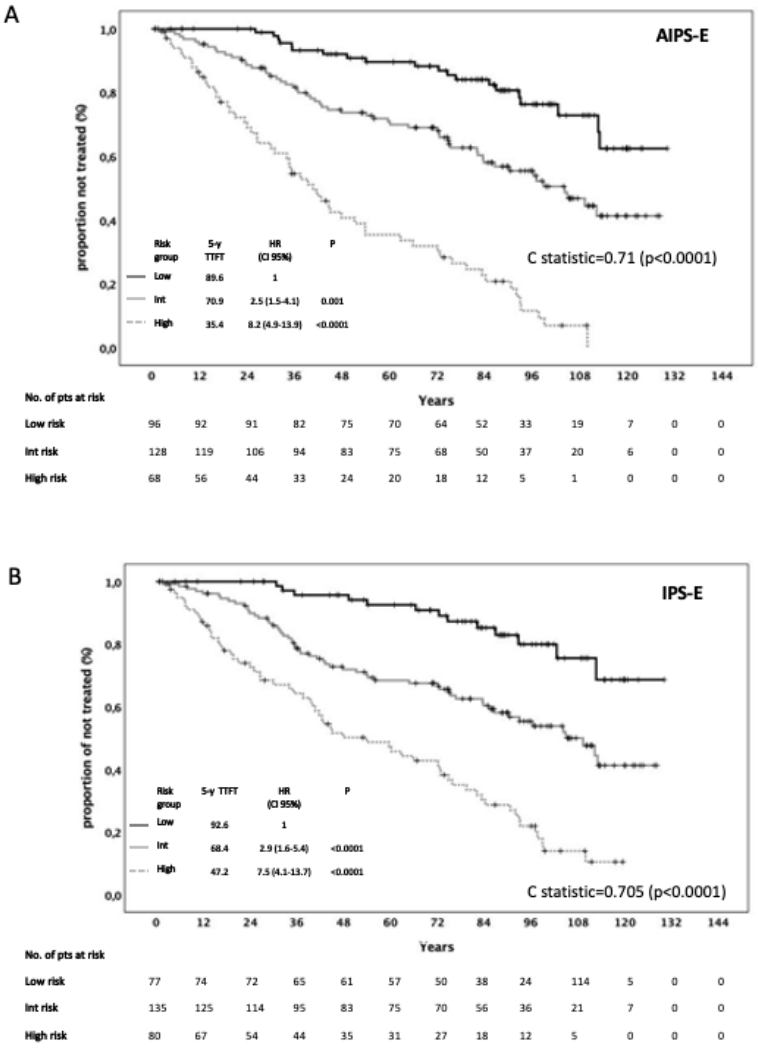

Figure 1

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